Cardiovascular events following renal transplantation: Role of traditional and transplant-specific risk factors

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Cardiovascular mortality is increased in transplant recipients. However, studies including non-fatal events are critical to assess the burden of disease and to identify novel risk factors. We described the incidence of fatal and non-fatal events, and explored associations and interactions among traditional and transplant-specific risk factors and cardiovascular events (CVE) in a cohort of 922 patients transplanted between 1993 and 1998. One hundred and seventy-six patients experienced 201 CVE (111 cardiac, 48 cerebrovascular, 42 peripheral-vascular). Most CVE were non-fatal. Factors associated with cardiac events were (adjusted hazard ratios) tobacco (3.53; $P<0.001$), obesity (2.92; $P<0.001$), diabetes (2.63; $P<0.001$), multiple rejections (2.19; $P=0.008$), prior CVE (2.0; $P=0.004$), dialysis >1 year (1.91; $P=0.007$), and overweight status (1.68; $P=0.04$); with cerebrovascular events: diabetes and peritoneal dialysis (11.95; $P<0.001$), age >45 (6.77; $P<0.001$), diabetes (4.87; $P<0.001$), prior CVE (3.73; $P<0.001$), creatinine >141 μmol/l (3.16; $P=0.001$), peritoneal dialysis (3.06; $P=0.027$), and obesity (0.32; $P=0.046$); with peripheral-vascular events: diabetes (8.48; $P<0.001$), tobacco and cytomegalovirus (3.88; $P<0.001$), age >45 (2.31; $P=0.019$), and prior CVE (2.25; $P=0.016$); with mortality: tobacco and deceased-donor (3.52; $P<0.001$), age >45 (1.81; $P=0.002$), diabetes (1.76; $P=0.002$), pulse pressure (1.64; $P=0.029$), prior CVE (1.52; $P=0.04$), and dialysis >1 year (1.47; $P=0.04$). The majority of CVE post-transplant were non-fatal. Previous CVE was strongly associated with CVE post-transplant. Interactions among transplant-specific and traditional risks impacted significantly the incidence of CVE. Modifiable factors such as duration of dialysis, deceased-donor transplantation, and acute rejection should be viewed as cardiovascular risks.

Kidney International (2006) **70,** 757–764. doi:10.1038/sj.ki.5001628; published online 21 June 2006

KEYWORDS: kidney transplantation; cardiovascular diseases; risk factors; cytomegalovirus

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Received 28 November 2005; revised 10 February 2006; accepted 1 March 2006; published online 21 June 2006

Patients with chronic kidney disease are at increased risk for premature cardiovascular disease and mortality associated with cardiovascular events (CVE).[1] Similar to the general population, the majority of deaths following renal transplantation are due to CVE. Analysis of traditional cardiovascular risks failed to explain the increased incidence of CVE experienced by the transplant population;[2] thus, it is speculated that a unique set of factors are responsible for this phenomenon. Furthermore, detailed analyses of interactions between traditional and transplant-specific factors have not been explored.

Mortality owing to cardiovascular disease has decreased steadily in the United States over the last decade, despite a simultaneous increase in its incidence,[3] a phenomenon explained by improvements in acute care of individuals experiencing CVE. Such changes in the profiles of outcomes may result in underestimation of the burden of cardiovascular disease, if mortality is the sole end point studied. National transplant registries, although containing detailed demographic variables and survival data, are less reliable sources for outcomes such as non-fatal CVE. In addition, owing to variable insurance coverage and restricted Medicare entitlement following transplantation, the United States Renal Data System (USRDS) has limited long-term transplant follow-up data. Finally, publications using large databases have failed to adjust their models for important pre-existing conditions, such as history of CVE or tobacco smoking before transplantation.[4,5]

To address these pitfalls, we conducted a single-center cohort study utilizing a closely monitored renal transplant population where cardiovascular outcomes data have been collected in a prospective fashion over a period longer than a decade. The main goals of this study were (1) to describe the incidences of fatal and non-fatal CVE, further categorized as cardiac, cerebrovascular, and peripheral vascular events; and (2) to describe interactions among traditional and transplant-specific cardiovascular risk factors in the incidence of CVE post-transplantation.

RESULTS

Between 1 January 1991 and 31 December 1998, 950 transplants were performed on 922 patients (26 patients

received two and one patient three transplants during the observation period). Mean age at transplantation was 44.2 ± 0.4 (s.e.m.) years, mean systolic and diastolic blood pressure were 136.6 ± 0.64 and 82.7 ± 0.39 mm Hg respectively, and the mean cholesterol level at transplantation was 5.3 ± 0.05 mmol/l (204.8 ± 1.8 mg/dl). A mean of 23.3 ± 0.98 months was described for those patients on dialysis before transplantation. Table 1 shows additional demographics data. All patients were accounted for the first year and 17 (1.8% of the cohort) were lost to follow-up at the 5-year time point. A total of 6947 patient-years of follow-up were accrued during the study period.

One hundred and seventy-six patients (19%) experienced 201 CVE (4.42 events per 100 patient-years). One hundred and eleven patients had a cardiac event (65 myocardial infarcts, 18 coronary artery bypasses, 16 angioplasties, and 12 new-onset angina pectoris), 48 a cerebrovascular event (39 cerebrovascular accidents, six transient ischemic attacks, and three carotid endarterectomies), and 42 a peripheral-vascular event (22 amputations, 18 revascularizations, and two new-onset claudications). One hundred and ninety-two patients (21%) expired, 56 (29%) deaths were owing to CVE (39 cardiac deaths and 17 cerebrovascular deaths; 1.23 fatal CVE per 100 patient-years). Seventy-one percent of CVE did not result in death (35% of cardiac events, 35% of cerebrovascular events, and none of peripheral-vascular events were recorded within 30 days of the recorded date of death). Of the cardiac deaths 12 occurred within 30 days of a myocardial infarct (seven deaths) or a revascularization procedure (five deaths). The remaining cardiac deaths, were determined by review of death certificates.

Table 2 shows the results of the univariate analysis for the primary outcome**:** transplantation after 1995, age older than 45, male gender, deceased-donor transplant, delayed graft function (DGF), history of diabetes, tobacco smoking, and CVE before transplantation were associated with increased risk for cardiac events after transplantation. Obese individuals, those within the highest tertile of pulse pressure at transplantation, and those on dialysis longer than 1 year also experienced more cardiac events. Hypercholesterolemia and hypertension because of their biological significance, were entered in the multivariable models. In the complete model (Table 3), prior CVE, diabetes, tobacco smoking, obesity, multiple rejections, and dialysis >1 year were significant independent variables associated with cardiac events following renal transplantation. The 'best-fit' reduced model (Table 4) identified tobacco smoking, obesity, pre-existing diabetes, multiple rejection episodes, prior CVE, overweight status, and dialysis >1 year as significant risk factors. Age >45 and a single rejection episode were not independently associated with cardiac events but contributed to the best-fit of the model. Body mass index was also significant when entered in the model as a continuous variable (adjusted hazard ratio 1.08; 95% confidence interval (CI) 1.04–1.13; $P<0.001$).

Table 1 | Demographics of the study cohort

Variable	Categories	*N* (%)
Year of transplantation	1991–1994	444 (48)
	1995–1998	478 (52)
Age (at transplantation)	18–45 years	495 (54)
	>45 years	427 (46)
Gender	Female/male	402 (44)/520 (56)
Ethnicity	Caucasian	786 (85)
	Black	40 (4.3%)
	Hispanic	37 (4%)
	Asians or other	59 (6.4%)
Transplant number	1/>1	791 (86%)/131 (14%)
Type of donor	Living/deceased	243 (26%)/679 (74%)
Diabetes pre-transplant	Yes	265 (28.1%)
Tobacco before transplant	Yes	319 (34.6%)
Prior cardiovascular event	Yes	152 (16.5%)
BMI (at transplantation)	Normal (lower than 25 kg/m^2)	503 (54.6%)
	Overweight (25–30 kg/m^2)	279 (30.2%)
	Obese (greater than 30 kg/m^2)	140 (15.2%)
Dialysis duration	No dialysis	153 (16.6%)
	Dialysis <1 year	277 (30%)
	Dialysis >1 year	492 (53.4%)
Modality of dialysis	Hemodialysis	491 (53.2%)
	Peritoneal dialysis	198 (21.5%)
	Both	80 (8.8%)
Prior CMV infection	Yes	563 (61.1%)
Beta blocker	Yes	174 (18.9%)
Diuretic	Yes	83 (9%)

BMI, body mass index; CMV, cytomegalovirus.

Explanatory variables associated with cerebrovascular events in the univariate analyses included age >45 ($P<0.001$), diabetes ($P<0.001$), prior CVE ($P<0.001$), peritoneal dialysis ($P=0.002$), deceased-donor transplant ($P=0.005$), hypercholesterolemia ($P=0.02$), cytomegalovirus (CMV) infection ($P=0.03$), and elevated pulse pressure at 3 months ($P=0.03$). An elevated 3-month creatinine level ($P=0.08$), re-transplantation status ($P=0.11$), dialysis >1 year ($P=0.13$), transplantation after 1994 ($P=0.12$), and obesity at transplantation ($P=0.19$) were also included in the models. An interaction between peritoneal dialysis and diabetes mellitus was detected. Therefore, an interaction term diabetes*peritoneal dialysis was entered in the multivariable

Table 2 | Cardiac events (results of the univariate analysis)

Variable	Categories	*n*	Events	Event-free survival			*P*-value
				1 year	3 years	5 years	
Transplant era	1991–1994	444	53	97	95	92	—
	1995–1998	478	58	96	93	89	0.037
Age at transplant	Younger than 45	495	44	98	96	93	—
	45 and older	427	67	95	92	87	0.007
Gender	Female	402	39	97	94	92	—
	Male	520	72	97	94	89	0.047
Transplant number	First	791	96	97	94	90	—
	Retransplant	131	15	98	93	90	0.82
Donor type	Living	243	16	98	97	94	—
	Deceased	679	95	96	93	89	0.017
Prior CMV infection	No	354	39	97	95	92	—
	Yes	563	72	96	93	89	0.49
Graft function	Immediate	704	77	98	95	92	—
	Delayed	218	34	93	89	85	0.003
Diabetes pre-transplant	No	657	56	98	95	93	—
	Yes	265	55	95	90	84	<0.001
Tobacco pre-transplant	No	603	43	98	96	94	—
	Yes	319	68	95	90	83	<0.001
Prior cardiovascular event	No	770	66	98	96	93	—
	Yes	152	45	90	84	75	<0.001
Obesity at transplant	Normal	503	42	98	97	94	—
	Overweight	279	39	95	92	89	—
	Obese	140	30	94	90	83	<0.001
Hypertension at transplant	No	404	44	97	94	91	—
	Yes	518	67	97	93	90	0.28
Hypertension at 3 months	No	388	36	99	97	94	—
	Yes	433	44	99	95	92	0.67
High cholesterol at transplant	No	445	47	97	95	92	—
	Yes	456	59	97	94	90	0.38
High cholesterol at 3 months	No	177	16	99	97	91	—
	Yes	664	70	99	96	93	0.65
Duration of dialysis	No dialysis	153	12	98	96	93	—
	Less than 1 year	277	22	97	96	95	—
	Longer than 1 year	492	77	96	92	87	0.007
Rejection at 3 months	None	576	53	99	97	93	—
	Single	173	20	99	96	91	—
	Multiple	112	16	98	93	90	0.16
Creatinine at 3 months	124 or lower	370	38	98	95	92	—
	125–141	223	21	99	98	94	—
	142 or higher	264	28	99	96	93	0.74
Pulse pressure at transplant	48 or lower	310	29	98	95	92	—
	49–60	305	36	96	93	91	—
	61 or higher	307	46	97	93	88	0.036
Pulse pressure at 3 months	45 or lower	245	23	99	96	93	—
	46–58	306	26	99	97	94	—
	59 or greater	270	31	99	95	91	0.39

Table 2 continued on the following page

Table 2 | Continued

Variable	Categories	n	Events	Event-free survival 1 year	3 years	5 years	P-value
Type of calcineurin inhibitor	Cyclosporine	781	91	97	95	91	—
	Tacrolimus	109	12	94	92	89	0.15
Modality of dialysis	Hemodialysis	491	70	96	93	89	—
	Peritoneal dialysis	198	20	97	95	92	—
	Both	80	13	96	93	88	0.29

CMV, cytomegalovirus.

Table 3 | Cardiac events post-transplant (multivariable analysis, complete model)

Variable	Hazard ratio[a]	95% CI	P-value
Prior cardiovascular event	4.59	2.56–8.25	<0.001
Diabetes mellitus	3.94	2.37–6.55	<0.001
Tobacco history	2.89	1.92–4.34	<0.001
Obesity at transplant	2.67	1.60–4.45	<0.001
Multiple rejections	2.05	1.13–3.70	0.02
Dialysis >1 year	1.79	1.15–2.80	0.01
Overweight at transplant	1.54	0.98–2.43	0.06
Single rejection	1.43	0.84–2.42	0.19
Transplant after 1994	1.38	0.89–2.12	0.14
Delayed graft function	1.23	0.78–1.93	0.38
Deceased donor	1.23	0.69–2.18	0.49
Male gender	1.14	0.75–1.72	0.54
Age older than 45 years	1.11	0.72–1.71	0.64
Hypercholesterolemia	1.08	0.73–1.60	0.71
Pulse pressure at transplant	1.05	0.53–1.87	0.9
Immunosuppression (cyclosporine)	0.98	0.47–1.77	0.9

CI, confidence interval.
[a]Hazard ratios adjusted by all the variables listed.

Table 4 | Cardiac events occurring post-transplant (best-reduced model)

Variable	Hazard ratio[a]	95% CI	P-value
Tobacco history	3.53	2.26–5.53	<0.001
Obesity at transplant	2.92	1.69–5.04	<0.001
Diabetes mellitus	2.63	1.70–4.09	<0.001
Multiple rejections	2.19	1.27–3.92	0.008
Prior cardiovascular event	2.00	1.25–3.18	0.004
Dialysis >1 year	1.91	1.20–3.05	0.007
Overweight at transplant	1.68	1.02–2.76	0.04
Age older than 45 years	1.57	0.99–2.38	0.054
Single rejection	1.43	0.85–2.42	0.18

CI, confidence interval.
[a]Hazard ratios adjusted by the other variables listed in the table.

Table 5 | Cerebrovascular, peripheral-vascular events, and mortality (best-reduced models)

Variable	Hazard ratio[a]	95% CI	P-value
Cerebrovascular events			
Diabetes and peritoneal dialysis	11.95	5.01–28.47	<0.001
Age >45 years	6.77	3.06–14.98	<0.001
Diabetes	4.87	2.07–11.48	<0.001
Prior cardiovascular event	3.73	1.93–7.21	<0.001
Creatinine >141 μmol/l	3.16	1.59–6.30	0.001
Peritoneal dialysis	3.06	1.14–8.26	0.027
Obesity at transplantation	0.32	0.11–0.98	0.046
Overweight at transplant	0.51	0.25–1.04	0.063
Transplant after 1994	0.52	0.26–1.04	0.066
Peripheral-vascular events			
Diabetes pre-transplant	8.48	3.97–18.1	<0.001
Tobacco and prior CMV infection	3.88	2.06–7.31	<0.001
Age >45 years	2.31	1.14–4.66	0.019
Prior cardiovascular event	2.25	1.17–4.35	0.016
Peritoneal dialysis	2.13	0.71–6.42	0.18
Mortality			
Tobacco and deceased donor	3.52	1.97–6.31	<0.001
Age >45 years	1.81	1.25–2.63	0.002
Diabetes pre-transplant	1.76	1.24–2.51	0.002
Pulse pressure of 61 mm Hg or greater	1.64	1.05–2.55	0.029
Prior cardiovascular event	1.52	1.02–2.26	0.04
Dialysis >1 year	1.47	1.02–2.12	0.04
Hypercholesterolemia at transplant	0.7	0.50–1.00	0.05

CI, confidence interval; CMV, cytomegalovirus.
[a]Hazard ratios adjusted by the other variables listed in the table.

models. The 'best-fit' reduced model included diabetes and peritoneal dialysis, age >45, diabetes, prior CVE, serum creatinine above 141 μmol/l (1.6 mg/dl) at 3 months (upper tertile), peritoneal dialysis, and obesity (Table 5). Transplantation after 1994 and overweight status also contributed to the fit of the model.

Peripheral-vascular events post-transplant were associated with age >45 ($P=0.009$), diabetes ($P<0.001$), tobacco smoking ($P=0.001$), previous CVE ($P<0.001$), peritoneal dialysis ($P=0.012$), and male gender ($P=0.05$). Prior CMV ($P=0.11$), DGF ($P=0.15$), and pulse pressure at 3 months ($P=0.19$) were entered in the multivariable models. The only potential interaction was between prior CMV infection and tobacco smoking (Figure 1): hazard ratios 1.3 (0.45–2.82), 2 (0.59–4.56), and 6 (2.25–10.01), non-smoker + CMV positive, smoker + CMV negative, and smoker + CMV positive, respectively. The best-reduced model included diabetes, prior CMV infection and tobacco smoking, age >45, and prior CVE. Peritoneal dialysis contributed to the best fit of the model (Table 5).

Variables associated with mortality were age >45 ($P<0.001$), deceased donor ($P<0.001$), DGF ($P<0.001$), diabetes ($P<0.001$), tobacco smoking ($P<0.001$), prior CVE ($P<0.001$), dialysis >1 year ($P<0.001$), and elevated pulse pressure at transplantation ($P=0.006$). Repeated rejections

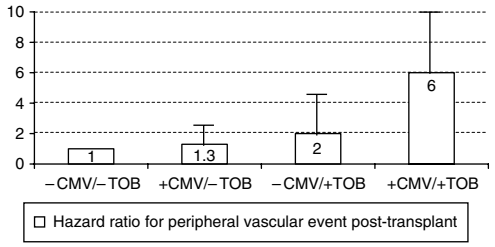

Figure 1 | Hazard ratios for post-transplant peripheral-vascular events. −CMV/−TOB = no prior CMV infection and no history of tobacco ($n = 243$), +CMV/−TOB = prior CMV infection and no history of tobacco ($n = 367$), −CMV/+TOB = no prior CMV infection and positive tobacco ($n = 126$), +CMV/+TOB = prior CMV infection and positive tobacco ($n = 186$).

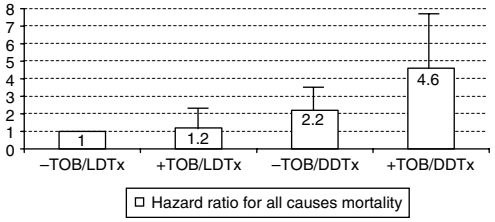

Figure 2 | Hazard ratios for death post-transplant. −TOB/LDTx = no history of tobacco and living-donor transplant ($n = 259$), +TOB/LDTx = positive tobacco and living-donor transplant ($n = 64$), −TOB/DDTx = no history of tobacco and deceased-donor transplant ($n = 385$), +TOB/DDTx = positive tobacco and deceased-donor transplant ($n = 214$).

within the first 3 months ($P = 0.057$), obesity ($P = 0.09$), peritoneal dialysis ($P = 0.1$), creatinine at 3 months ($P = 0.14$), hypertension ($P = 0.19$), gender, and hypercholesterolemia were also entered in the multivariable models. An interaction between tobacco smoking and type of organ donor was found (Figure 2): hazard ratios 1.2 (0.49–2.69), 2.2 (1.26–3.59), and 4.6 (2.69–7.86), smoker + live donor, non-smoker + deceased-donor, and smoker + deceased donor, respectively. The best-reduced model for patient death included history of tobacco smoking on recipients of a deceased-donor organ, age >45, diabetes, prior CVE, elevated pulse pressure, dialysis >1 year, and hypercholesterolemia. Duration of dialysis was also significant when entered in the model as a continuous variable (adjusted hazard ratio: 1.07; 95% CI 1.02–1.11; $P = 0.004$).

DISCUSSION

Cardiovascular mortality is increased in patients with chronic kidney disease.[6–8] Mortality from cardiovascular disease is 10–20 times higher among individuals treated with dialysis, as compared to general population.[1] The incidence of cardiovascular disease in kidney transplant patients is nearly twice that of the general population.[9] Even young transplant recipients (aged 35–45 years) experienced an almost 10-fold increase in cardiovascular disease-related mortality.[1] Reducing deaths from cardiovascular disease in persons with chronic kidney disease is one of the Healthy People 2010 objectives.[10] Risk factors associated with cardiovascular disease after transplantation are similar to those described in population-based studies. However, when traditional cardiovascular risk scores were applied to a cohort of transplant recipients, the risks clearly underestimated the incidence of CVE,[2] suggesting that other transplant-specific factors may contribute to cardiovascular risk either independently or by interacting with traditional factors.[11] Our study analyzed the relationships among traditional and transplant-specific risk factors and cardiovascular outcomes, described in categories of affected vasculature: cardiac, cerebral, and peripheral. Fatal and non-fatal events were studied and two-way interactions among explanatory variables were included in the analyses.

This report describes associations involving prior CVE and ischemic events post-transplant in all categories of vasculature. Until recently,[12] prior CVE have not been accounted for in studies addressing post-transplant CVE. This factor assumes particular importance as the proportion of individuals with co-morbid cardiovascular disease at the time of transplantation has increased from 40% in 1995 to 50% in 2001.[13]

Interaction terms are used to describe effect-measure modifications. In other words, an exposure may result in heterogeneous effects in different strata of subjects. The importance of analysis of such interactions as a tool to uncover novel-risk factors is exemplified in our report. It has been described that recipients of a deceased-donor organ experience higher incidence of CVE than living-donor recipients.[13] However, we were able to expand such observation by describing interactions among tobacco and deceased-donor transplantation in overall mortality, and between tobacco and CMV infection in the incidence of peripheral-vascular events. The association between CMV infection and CVE following transplantation has been controversial.[14–16] Reactivation of latent CMV in endothelial cells of arteries may contribute to atherogenesis.[17] CMV genetic material and antigens have been detected in endothelial and deeper layers of diseased human aortas by *in situ* hybridization and immunohistochemical staining,[18] and in arterial vessels from diabetics undergoing amputations.[19] Antibodies against CMV crossreact with a human heat-shock protein and cause endothelial cell death *in vitro*.[20] These phenomena may provide the pathophysiologic basis for the association between CMV infection and arteriosclerosis. The role of tobacco smoking in modulating such disease process should be a target for further research.

Description of an association between renal dysfunction and cardiovascular disease has been published 15 years ago.[21] In the Framingham Heart Study a trend towards an association between minor renal dysfunction and future cardiovascular morbidity and mortality was described.[6] Data from the NHANES II have revealed an association between mild-to-moderate renal insufficiency and increased cardiovascular mortality, which was independent from other traditional risk factors such as diabetes, smoking, or

dyslipidemia.[22] These findings have been confirmed in large populations such as the Northern California Kaiser-Permanente,[23] HOT,[24] HOPE,[25] and VALIANT[26] cohorts. Associations between decreased renal function at 1 year post-transplantation and hospitalizations owing to acute coronary syndromes or chronic heart failure[4] and mortality[5] have been described. We expand these observations by describing an association between serum creatinine levels and cerebrovascular events post-transplantation. Associations between mild renal dysfunction and cerebrovascular events have been described in a community-based study[27] and in a large interventional trial.[26] However, to date, no description of such association has been reported following renal transplantation, including in an interventional trial using fluvastatin following transplantation.[28] The association between loss of allograft function (with return to dialysis) and CVE has been described previously.[29] In our study, 181 patients lost their graft during the observation period. Survival data were censored at the time of a repeated transplant (38 patients). Twenty-nine patients are known to have expired on dialysis. Cardiac events were recorded in nine of these patients (seven cardio-respiratory arrests and two myocardial infarcts vs acute coronary syndrome). Censoring patients at the time of allograft failure did not change our results significantly.

Associations between obesity at transplantation and chronic heart failure[4] and cardiovascular mortality[30] have been described previously. However, an association between elevated body mass index and ischemic heart disease has not. In our study, obesity was associated with cardiac events with a suggestion of a dose–response phenomenon. The same data suggest that obesity might have a reverse association with cerebrovascular events. A competing risks phenomenon could have played a role in such association (i.e., if a number of obese individuals would die from other causes soon after transplantation, a lower proportion would continue to be at risk for cerebrovascular events later on). However, no associations between obesity and death either on univariate or multivariable analyses were found (1 year patient survival was 98, 95, and 96%, for normal, overweight, and obese, respectively).

The association between duration of dialysis and cardiovascular mortality has been described.[4,5,31] In our cohort study, dialysis longer than 1 year before transplant was associated not just with mortality but also with non-fatal cardiac events. A fivefold increased risk for cerebrovascular events in chronic dialysis patients as compared to the general population has been described,[32] and peritoneal dialysis has been associated with higher incidence of hospitalizations for cardiovascular complications, when compared with hemodialysis.[4] It has been suggested that peritoneal dialysis is offered to older patients with a greater number of co-morbid conditions. This factor could have introduced a selection bias in our cohort; however, age (44.7 ± 11.88 vs 44.1 ± 12.03 years; $P = 0.4$) and prevalence of CVE before transplant (17 vs 19.5%; peritoneal vs hemodialysis respectively; $P = 0.06$) were not different. Furthermore, if a selection bias was present, we should have observed a higher incidence of cardiac events or deaths in this group, which was not noted in our results.

Observational studies are not without limitations. Socioeconomic status has been described as an independent cardiovascular risk. Unfortunately, our database has incomplete data on such variable. Further data on the amount and duration of tobacco exposure would be needed to establish a dose–response curve. A larger cohort and longer observation period would allow for analyses of additional risk factors and provide enough statistical power to further explore subtle interactions. A more diverse cohort would allow analysis of exploratory variables across ethnicities. Our report included cardio-respiratory arrest as extracted from the death certificates as part of the primary outcome. Recently, a different profile of risk factors for either ischemic or non-ischemic cardiac events has been discussed.[33] Unfortunately, owing to the limited sample size and few potential non-ischemic events (i.e., sudden deaths), these differences could not be further evaluated using our cohort. The impact of a non-fatal event occurring post-transplant on overall mortality should be explored using a different analytical strategy such as time-dependent Cox models.

In conclusion, our study has shown that (1) the majority of CVE were indeed non-fatal, supporting our hypothesis that mortality data underestimate the burden of cardiovascular disease in this population; (2) CVE before transplantation is a strong factor associated with all categories of CVE post-transplant (transplant patients carry a burden of pre-existing cardiovascular disease); (3) interactions among transplant-specific and traditional risks have a significant impact on the incidence of CVE post-transplant, suggesting that a combination of clinical and laboratory variables could lead to the development of a cardiovascular risk-scoring tools unique to this population. Furthermore, risk factors such as duration of dialysis, deceased-donor transplantation, CMV infection (and prophylaxis), and acute rejection episodes should be viewed not just as risk factors for allograft failure but also as cardiovascular risk factors and as targets for further research and interventions.

MATERIALS AND METHODS

Detailed information on more than 3300 renal transplants at Oregon Health and Science University has been collected prospectively and entered into a secured database since 1978. The study cohort includes all adult transplanted between 1 January 1991 and 31 December 1998. This period was chosen to provide a minimal follow-up of 5 years and a sample size large enough to allow inclusion of several explanatory variables in the multivariable models. Patients were followed weekly or bi-weekly for the first 3 months, monthly from months 4 to 6, every 6 months from month 7 to 36 following transplantation, and yearly thereafter. The standard triple immunosuppressive therapy used during the study period consisted of a calcineurin inhibitor (either cyclosporine A or tacrolimus), azathioprine, and prednisone. Since 1999, mycophenolate mofetil has been used as a substitute for azathioprine in about

20% of our cohort, mainly in those with high immunologic risk (i.e., repeated transplants, high PRA recipients, and those who experienced delayed onset of graft function or acute rejections within the first year of transplantation). Beta blockers and diuretics were used at some point in 18.9 and 9% of recipients, respectively. Data on angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and aspirin were not available in the database.

The primary outcome of interest in the study was time to cardiac event, defined as: length of time between transplantation and the date of new-onset angina pectoris, acute myocardial infarct, coronary angioplasty or bypass surgery, or cardiac death (by death certificate). Acute myocardial infarction was defined according to the consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction,[34] and other cardiac events were ascertained by chart reviews of hospital discharge summaries and procedure records (including angiograms and reports from percutaneous interventions and surgical revascularizations). Secondary outcomes were (1) time to cerebrovascular event (time span from transplantation to first transient ischemic attack, cerebrovascular accident, carotid endarterectomy or angioplasty, or death from a cerebrovascular event), (2) time to peripheral-vascular event: time to new-onset claudication (confirmed by angiography), limb revascularization, or amputation, and (3) patient survival. A CVE was considered fatal if death was recorded within 30 days of a CVE date. The date of last follow-up was the date of last input in the database (clinic visit, laboratory data, or death date). Patients were censored at the date of last follow-up (up to 30 June 2004), if no events were observed. To ascertain accuracy of mortality data, a Social Security Administration Death Master File search was conducted in 30 October 2004 including the entire cohort.

Traditional cardiovascular risks factors analyzed were age, gender, blood pressure (systolic, diastolic, and pulse pressures), cholesterol, presence of diabetes, obesity, tobacco smoking, and history of CVE before transplantation. Transplant-specific risk factors were time spent on and modality of dialysis before transplantation, DGF previous CMV infection, type of organ donor (living or deceased), immunosuppressive regimen, acute rejection episodes, and serum creatinine at 3 months post-transplant. Body mass index was calculated by the formula weight (kilograms)/square of height (meters), and was analyzed both as continuous and as categorical variables (low to normal: $<25\,kg/m^2$; overweight: 25–30 kg/m^2; obese: $>30\,kg/m^2$). Pulse pressure was calculated by subtracting the diastolic from the systolic blood pressures and also analyzed as continuous and categorical variables (tertiles). Hypertension was defined by a systolic >140 mm Hg, a diastolic >90 mm Hg, or the use of antihypertensive drugs. Hypercholesterolemia was defined by fasting total cholesterol >5.2 mmol/l (>200 mg/dl) or by the use of lipid-lowering drugs. Categories of modality of dialysis were none, hemodialysis, peritoneal dialysis, or both. DGF was defined by dialysis within the first week post-transplant. Immunosuppression was categorized by the type of calcineurin inhibitor (cyclosporine or tacrolimus). Continuous variables were entered as such in the models or were transformed into categories either by using tertiles (pulse pressure and creatinine levels) or by using cutoff levels based on previous publications (age, body mass index, and time on dialysis). The decision to describe a variable either as continuous or categorical was based on the best fit of the multivariable models. With the exception of death, other CVE were not mutually exclusive. Event-free survival curves were constructed using the product-limit method (Kaplan–Meier). Differences among survival curves were estimated by the log rank test. Cox proportional hazards models were built using variables with a *P*-value lower than 0.2 in the univariate analyses, and variables considered to be of biological significance (age, gender, hypertension, hypercholesterolemia, previous CVE, tobacco smoking, and diabetes). Direct visualization of log(−log (survival time)) vs log (survival time) plots was used to validate the proportionality of hazard increments assumption. Results were reported as hazard ratios with correspondent 95% CI and *P*-values. Pre-established two-way interactions between each of the transplant-specific variables and traditional risk factors were screened and, if significant, entered into the multivariable models. The significance of a cluster of independent variables was analyzed by using the likelihood-ratio test. Single variables were removed from the complete models and the ratios of the likelihoods of the reduced models to the complete models were calculated on a stepwise fashion. Best-fit reduced models were found once no further variables could be removed. *P*-values lower than 0.05 (two tailed) were considered significant. SPSS 11.5 for windows (SPSS® Inc., Chicago, IL, USA) was used in the analysis. The protocol was approved by the local institution review board.

ACKNOWLEDGMENTS

We thank Dr Robert S Gaston for a critical review of this paper. None of the authors has declared a conflict of interest in relation with the paper. Abstract presented at American Transplant Congress 2005.

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